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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,356	12/28/2004	Bertram Cezanne	MERCK-2952	4530

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EXAMINER	
KOSACK, JOSEPH R	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 09/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/519,356	CEZANNE ET AL.	
	Examiner	Art Unit	
	Joseph Kosack	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *4,5 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,28,31,33,52,53 and 57* is/are rejected.

7)☒ Claim(s) *1-3,6-26,29,30,33-51,54-56 and 58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-58 are pending in the instant application.

Amendments

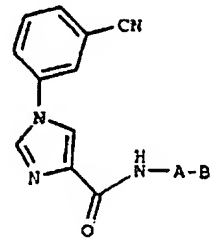
The amendment filed on July 20, 2006 has been acknowledged and has been entered into the record.

Election/Restrictions

Applicant elected Group I in the reply filed February 17, 2006. The lack of unity requirement made on January 17, 2006 was made final in the action mailed April 20, 2006.

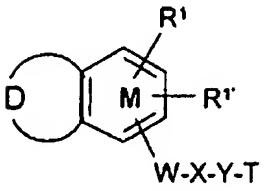
Applicant has retraversed the requirement on the grounds that the imposition of a lack of unity requirement of a Markush group is improper under 35 U.S.C. 121 since no Markush rejection was made, that the compounds as claimed have a significant core structure and therefore have unity of invention, and that the requirement was in actuality an election of species requirement and that the search is required to be expanded to determine patentability of the entire invention as claimed is required.

The determination of lack of unity may be viewed in one of two ways. The first way is that all of the structures of group M contained a conjugated 6-membered ring structure with a ring structure attached to the M-ring. Since R1 and R1' can be hydrogent and the M-D ring system and W-X-Y-T group can have vastly differing meanings, the core structure was determined to be a ring structure attached to the M-conjugated 6-membered ring. WO 98/28269 teaches such a structure:



. See page 57. Therefore, the technical feature does not make a contribution over the art, and unity is lacking.

The second way of determining lack of unity is to look at the original Formula I:



. Since each substituent can be different, there is no discernable special technical feature of the inventions as a whole. Therefore, unity of invention is lacking. See Example 24 of Chapter 10 of the International Search and Preliminary Examination Guidelines:

10.44 *Example 24*

Claim 1: A pharmaceutical compound of the formula:

$$A-B-C-D-E$$

wherein:

A is selected from C_1-C_{10} alkyl or alkenyl or cycloalkyl, substituted or unsubstituted aryl or C_5-C_7 heterocycle having 1-3 heteroatoms selected from O and N;

B is selected from C_1-C_6 alkyl or alkenyl or alkynyl, amino, sulfoxy, C_3-C_8 ether or thioether;

C is selected from C_5-C_8 saturated or unsaturated heterocycle having 1-4 heteroatoms selected from O, S or N or is a substituted or unsubstituted phenyl;

D is selected from B or a C_4-C_8 carboxylic acid ester or amide; and

E is selected from substituted or unsubstituted phenyl, naphthyl, indolyl, pyridyl, or oxazolyl.

From the above formula no significant structural element can be readily ascertained and thus no special technical feature can be determined. Lack of unity exists between all of the various combinations. The first claimed invention would be considered to encompass the first mentioned structure for each variable, that is, A is C_1 alkyl, B is C_1 alkyl, C is a C_5 saturated heterocycle having one O heteroatom, D is C_1 alkyl, and E is a substituted phenyl.

Therefore, it was proper to define groups under a lack of unity requirement by particular compounds since there was no significant structural element that could be ascertained that was common to all of the various compounds that fall under the scope of such a claim. As a courtesy to the Applicant, the Examiner expanded the elected group to define a core structure that encompasses the elected group.

As to Applicant's assertion that restriction within a claim is improper based on 35 U.S.C. 121 and the interpretation by the court in *in re Weber* (198 USPQ 328), Applicant is reminded that lack of unity is not covered by 35 U.S.C. 121, but by 35 U.S.C. 372 and PCT rules 13.1 and 13.2. Also, the citation of *in re Weber* and chapter 800 of the MPEP is immaterial as shown by MPEP 801:

801 Introduction

This chapter is limited to a discussion of the subject of restriction and double patenting under Title 35 of the United States Code and Title 37 of the Code of Federal Regulations as it relates to national applications filed under 35 U.S.C. 111(a). The discussion of unity of invention under the Patent Cooperation Treaty Articles and Rules as it is applied as an International Searching Authority, International Preliminary Examining Authority, and in applications entering the National Stage under 35 U.S.C. 371 as a Designated or Elected Office in the U.S. Patent and Trademark Office is covered in Chapter 1800.

Therefore, Applicant's arguments have been considered in their entirety, but were not found to be persuasive. The finality of the lack of unity requirement is maintained.

Status of the Claims

With the amendment filed July 20, 2006, claims 1-58 are now pending in the instant application with claims 45-58 as new claims. In the action mailed April 20, 2006, claims 1-3 (in part), 4-5, 6-31 (in part), 32, and 33-44 (in part) were withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 45-58 (in part) are now withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Previous Claim Objections

Claims 1-3, 6-31, and 33-44 were objected to in the action mailed April 20, 2006 for containing elected and non-elected subject matter. The amendment filed July 20, 2006 has not cancelled the non-elected subject matter, and the objection is maintained.

Previous Claim Rejections - 35 USC § 112

Claims 27-28, 31, and 33 were rejected in the action mailed April 20, 2006 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

treating thromboembolic disorders such as thrombosis and myocardial infarction, does not reasonably provide enablement for treating other diseases such as tumors and inflammation.

Applicant has traversed the rejection on the grounds that the evidence cited do not present reasons to doubt the presumption of an enabling disclosure and that undue experimentation is not required to practice the invention.

To the point that the evidence cited in the action mailed April 20, 2006 does not present reasons to doubt the presumption of an enabling disclosure, the Examiner respectfully disagrees. The amount of enablement support required within the original disclosure is inversely proportional to the predictability of the art at the time of the invention. Wong et al. (*Cardiovascular Drug Reviews 2002*, 137-152) and Sampson et al. (*Biochemical Society Transactions 2002*, 201-207) do not teach the use of anticoagulants as a tumor therapy, as stated in the previous action. Schulman et al. (*New England Journal of Medicine 2000*, 1953-1958) teach that the beneficial effects of treatment of small-cell lung cancer with the anticoagulant warfarin in a 1981 clinical trial have never been confirmed. Schulman et al. also teach that the addition of warfarin to treatment of small-cell lung cancer to a regimen of chemotherapy and radiation resulted in no improvement over chemotherapy and radiation alone. Applicant points out on page 21 of the response filed July 20, 2006 that Schulman et al. also states that their "findings strongly support the impression that warfarin has an antineoplastic effect," but fails to show the entire sentence which reads "Our findings strongly support the impression that warfarin has an antineoplastic effect, but this idea will remain controversial in the absence of a demonstrated biochemical explanation."

Applicant had cited articles to provide for support for the treatment of diseases other than thromboembolic disorders (pages 6-7 of the specification), and a sampling of the references was performed by the Examiner to test the level of support provided for the use of an anticoagulant for other therapies. The articles of Donnelly et al. (*Thromb. Haemost. 1998*, 1041-1047) only teach the link between factor Xa and TF/VIIa to tumor metastasis, but not to any reduction in tumor size, health, efficacy, etc... The teachings of Bromberg et al. (*Thrombosis and Haemostasis 1999*, 88-92.) show that no inhibitors of TF/VIIa were attempted, let alone the effects of a small molecule inhibitor of factor VIIa on the treatment of tumors. An example shows binding affinity to factors Xa and TF/VIIa of four compounds of the instant invention, but nothing is shown as to how the treatment of tumors can be accomplished. Also, it is unknown who the target population is for the method of inhibiting coagulation factors Xa and VIIa. Applicant supplied a copy of the Fischer et al. (*J. Clin. Invest. 1999*, 1213-1221), that teaches essentially the same results as provided by Donnelly et al. and Bromberg et al. Since treatment is defined by the person of skill in the art to include lessening the symptoms of, prevention of disease progression, prevention of worsening of symptoms, destruction of bacteria/viruses/cells causing the disease, etc..., the specification has not sufficiently enabled all of the possible definitions of treatment or treating as shown by the art of the time of invention.

Also, Applicant cited a document to provide enablement for the treatment of migrane (*Headache 2000*, 45-47), but the mechanism for improvement was unknown and the study has admitted several limitations.

The specification does provide evidence for how to use the compounds as pharmaceutical agents, but does not provide enablement as to how to make or use a method of treating a disease that is not a thromboembolic disorder.

As to the need or lack of need of undue experimentation, a showing of how to assay the activity of the compounds towards factor Xa or TF/VIIa is irrelevant without enablement for how inhibitors of factor Xa or TF/VIIa can fully treat diseases other than thromboembolic disorders. The experimentation that would be required at this point would constitute clinical trials, which would be undue experimentation in the view of the person of skill in the art.

Therefore, Applicant's arguments have been fully considered, but were not found to be persuasive. The rejection is maintained.

Claim Objections

Claims 1-3, 6-31, and 33-58 are objected to for containing elected and non-elected subject matter. The elected subject matter have been identified in the action mailed April 20, 2006.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-28, 31, 33, 52-53, and 57 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating thromboembolic disorders such as thrombosis and myocardial infarction, does not reasonably provide enablement for treating other diseases such as tumors and inflammation. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention is the inhibition of coagulation factors Xa (Claim 27) and VIIa (Claim 28), the treatment of specific diseases such as thromboses, myocardial infarction, and tumors without (Claim 31) and with an additional agent (Claim 33), the treatment of inflammation (Claim 52), apoplexia (Claim 53), and migrane (Claim 57).

The State of the Prior Art and the Predictability or Lack Thereof in the Art

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Wong et al. (*Cardiovascular Drug Reviews 2002*, 137-152) teach a compound that is structurally similar to the compounds of Formula I of the instant application as an inhibitor of coagulation factor Xa. Wong et al. only teach the connection between factor Xa to treating acute myocardial infarction, unstable angina, deep vein thrombosis, pulmonary embolism, and ischemic stroke. Sampson et al. (*Biochemical Society Transactions 2002*, 201-207) teach the role of factors VIIa and Xa in the blood coagulation cascade, but does not give any information on the importance of those specific factors in treating cancer, inflammation, or other diseases not associated with thrombosis. Schulman et al. (*New England Journal of Medicine 2000*, 1953-1958) teach that the beneficial effects of treatment of small-cell lung cancer with the anticoagulant warfarin in a 1981 clinical trial have never been confirmed. Schulman et al. also teach that the addition of warfarin to treatment of small-cell lung cancer to a regimen of chemotherapy and radiation resulted in no improvement over chemotherapy and radiation alone.

Applicant had cited articles to provide for support for the treatment of diseases other than thromboembolic disorders (pages 6-7 of the specification), and a sampling of the references was performed by the Examiner to test the level of support provided for the use of an anticoagulant for other therapies. The articles of Donnelly et al. (*Thromb. Haemost. 1998*, 1041-1047) only teach the link between factors Xa and TF/VIIa to

tumor metastasis, but not to any reduction in tumor size, health, efficacy, etc... The teachings of Bromberg et al. (*Thrombosis and Haemostasis 1999*, 88-92.) show that no inhibitors of TF/VIIa were attempted, let alone the effects of a small molecule inhibitor of factor VIIa on the treatment of tumors. An example shows binding affinity to factors Xa and TF/VIIa of four compounds of the instant invention, but nothing is shown as to how the treatment of tumors can be accomplished. Also, it is unknown who the target population is for the method of inhibiting coagulation factors Xa and VIIa. Fischer et al. (*J. Clin. Invest. 1999*, 1213-1221), teach essentially the same results as provided by Donnelly et al. and Bromberg et al. Since treatment is defined by the person of skill in the art to include lessening the symptoms of, prevention of disease progression, prevention of worsening of symptoms, destruction of bacteria/viruses/cells causing the disease, etc..., the specification has not sufficiently enabled all of the possible definitions of treatment or treating as shown by the art of the time of invention.

Also, Applicant cited a document to provide enablement for the treatment of migrane (*Headache 2000*, 45-47), but the mechanism for improvement was unknown and the study has admitted several limitations.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by inhibiting coagulation factors VIIa and Xa, one of skill in the art is unable to fully predict possible results from the administration of the compound of formula 1 due to the unpredictability of the role of inhibiting coagulation factors VIIa and Xa with respect to diseases other than thromboembolic disorders.

The Amount of Direction or Guidance Present and the Presence or Absence of Working Examples

The specification teaches the positive effects of inhibiting coagulation factors VIIa and Xa in treating thromboembolic disorders. The specification also cites certain references describing the antitumoral action of tissue factor TF/ factor VIIa and factor Xa inhibitors for various types of tumor. However, upon closer inspection of the cited teachings of Bromberg et al. (*Thrombosis and Haemostasis 1999*, 88-92.) no inhibitors of TF/VIIa were attempted, let alone the effects of a small molecule inhibitor of factor VIIa on the treatment of tumors. An example shows binding affinity to factors Xa and TF/VIIa of four compounds of the instant invention, but nothing is shown as to how the treatment of tumors can be accomplished. Also, it is unknown who the target population is for the method of inhibiting coagulation factors Xa and VIIa. As the claims read currently, it is believed that the target population is any living being since there is no definition of the patient population in the disclosure.

The Breadth of the Claims

The breadth of the claims is the the inhibition of coagulation factors Xa (Claim 27) and VIIa (Claim 28) of any living being, the treatment of specific diseases such as thromboses, myocardial infarction, and tumors without (Claim 31) and with an additional agent (Claim 33), and the treatment of inflammation (Claim 52), apoplexia (Claim 53), and migrane (Claim 57).

The Quantity of Experimentation Needed

The quantity of experimentation for the general inhibition of factors Xa and VIIa in a patient and for the treatment of diseases other than thromboembolic disorders needed

is undue experimentation. As to general inhibition of factors Xa and VIIA, one of ordinary skill in the art would have to determine what the patient population is that would benefit from the inhibition of those factors. Because of the uncertainty in the art to the treatment of diseases other than thromboembolic disorders with anticoagulants and factor Xa and VIIa inhibitors, undue experimentation would be necessary to test the efficacy of a method of treatment.

The Level of Skill in the Art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of formula 1 for the general inhibition of factors Xa and VIIa in a patient and for treating diseases other than thromboembolic disorders. As a result, necessitating one of skill to perform an exhaustive search for the proper patient population and any diseases other than thromboembolic disorders that can be treated by what compounds of formula 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome deleting the claims or by deleting the non-enabled portions of the method claims.

Conclusion

Claims 27-28, 31, 33, 52-53, and 57 are rejected. Claims 1-3, 6-31, and 33-58 are objected to. Claims 1-3, 6-31, and 33-58 are free of the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Kosack whose telephone number is (571)-272-5575. The examiner can normally be reached on M-F 5:30 A.M. until 2:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph R. Kosack

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